

Study Scrutinizes Safety of Teen Contraceptive Use

BY ELIZABETH MEHCATIE
Senior Writer

ROCKVILLE, MD. — No new safety concerns were raised by a review of adverse events reported during a recent 1-year period in adolescents taking a combination oral contraceptive, according to Jean Wendy Temeck, M.D., of the Food and Drug Administration's division of pediatric drug development.

The FDA's review of adverse events reported for Ortho Tri-Cyclen and Ortho Tri-Cyclen Lo, which contain norgestimate and ethinyl estradiol, was conducted between December 2003 and January 2005, the year after the FDA granted marketing exclusivity to the drug. Exclusivity is granted to a drug when companies perform pediatric studies of the product in exchange for a 6-month extension on the drug's patent.

In this case, the manufacturer, Ortho-McNeil Pharmaceutical Inc., conducted a placebo-controlled study to determine whether the OC improved bone density in adolescent girls with anorexia nervosa. The study showed no differences from placebo in increases in hip and lumbar-spine bone mineral density after 1 year of treatment.

Dr. Temek reported the data at a meeting of the FDA's Pediatric Advisory Committee. The Best Pharmaceuticals for Children Act requires that the FDA's Office of Pediatric Therapeutics review postmarketing adverse event reports made to the FDA's MedWatch adverse event reporting system during the year after a drug receives exclusivity. These reports are then referred to the Pediatric Advisory Committee for a review.

The uses of Ortho Tri-Cyclen for females 16 years of age and younger include dysfunctional uterine bleeding and acne, she said. During the postexclusivity period (Dec. 18, 2003, through Jan. 18, 2005) there were 14 unduplicated pediatric adverse event reports associated with Ortho Tri-Cyclen, including 11 serious reports and 0 deaths.

The 14 reports included 12 cases in adolescent girls and 2 cases involving infants that had been exposed in utero. Adverse events that were reported more than once were headaches and metrorrhagia, events that are listed in the label of Ortho Tri-Cyclen, and convulsions, an adverse event that is not in the label.

There were four hospitalizations, which included the two in utero exposures. The other two hospitalizations were in a 16-

year-old with benign intracranial hypertension, an increase in cerebrospinal fluid pressure, and a visual field defect; and in a 14-year-old who had cerebral thrombosis and headache. These two patients were also on isotretinoin.

A third patient who was also on isotretinoin, as well as prednisone, was reported to have depression, dizziness, and headache, which are unlabeled events for the OC; other symptoms included decreased interest, insomnia, and panic attack. (The labels for isotretinoin and prednisone include the risk of increased intracranial pressure, depression, insomnia, emotional instability, dizziness, and headache, Dr. Temeck noted.)

Of the two infants exposed in utero, one was in a breech presentation and born prematurely, and the baby's mother also had taken penicillin, betamethasone, and alprazolam while pregnant. The second exposed infant had cerebral artery occlusion, convulsion, apnea, and developmental delay.

There were three adolescents who reported visual adverse events, which are not mentioned in the Ortho Tri-Cyclen label: a 14-year-old also on oxcarbazepine who was reported to have papilledema and cluster headache; a 16-year-old also on

doxycycline and tretinoin, who had scotoma, blurred vision, headache, and influenza-like illness; and a 16-year-old also on isotretinoin and prednisone, who had a visual-field defect, in addition to benign intracranial hypertension and increased CSF pressure. (The label for Ortho Tri-Cyclen warns of retinal thrombosis.)

The other two serious adverse events were in one 14-year-old who developed hypertension and another 14-year-old who had dysarthria and hypoesthesia—two events not on the label. Convulsions also were reported in a 15-year-old who had a history of intermittent seizures.

Despite the reports of some serious adverse events reported during this period, "no pattern of new safety concerns" was identified, Dr. Temeck said. Based on the presentation, the advisory panel agreed with the FDA that monitoring of adverse events for these OCs could be switched to regular monitoring. ■

Health care professionals and consumers can report drug- or device-related adverse events to MedWatch by calling 800-332-1088, sending a fax to 800-332-0178, writing to MedWatch, Food and Drug Administration, 5600 Fishers Ln., Rockville, MD 20857-9787; or visiting www.fda.gov/medwatch.

Rare Side Effect of DMPA Seen in the Young

BY SHARON WORCESTER
Southeast Bureau

NEW ORLEANS — Decidual cast expulsion may occur in young patients using depot medroxyprogesterone acetate, Stephen M. Scott, M.D., said at the annual meeting of the North American Society for Pediatric and Adolescent Gynecology.

Although decidual casts are typically associated with ectopic pregnancy and can be confused with spontaneous abortion, Dr. Scott described four cases that suggest decidual casts might be a rare but important side effect associated with use of the hormonal contraceptive—particularly among those exposed after a prolonged period of anovulatory endometrial proliferation.

The first case involved a postanorexic 16-year-old girl who was on depot medroxyprogesterone acetate (DMPA) for contraception and presented 1 month after her first injection. She had a large amount of white tissue protruding from the cervical os. The patient had experienced weight recovery and signs of estrogen stimulation at the time of the injection, but also had persistent amenorrhea at the time of injection.

The second case involved a 20-year-old with cerebral palsy and mental retardation, who was using DMPA for the treatment of dysfunctional uterine bleeding. She presented with tissue passing from the vagina 3 weeks after her first injection.

The third case involved an 11-year-old with factor VIII deficiency, who was treated with DMPA to control hemorrhaging that occurred at her first menarche 8 months earlier. She presented with se-

vere cramps and the sensation of a mass in the vagina. An examination revealed white tissue protruding from the cervical os.

The fourth case involved a 19-year-old who had a vaginal delivery 5 months earlier and who at 3 months post partum was breast-feeding and amenorrheic. She began using DMPA for contraception at that time, and 2 months later, she presented with bleeding and cramping. As with the first three cases, examination revealed a large amount of tissue at the cervical os.

The findings in each case were consistent with decidual cast expulsion, and all patients had a negative result on a pregnancy test. The removal of the protruding tissue resulted in symptom resolution, said Dr. Scott of the University of Colorado, Denver.

Because decidual casts are rare, "we don't really have a great idea of what elements are needed in order to form a decidual cast and pass it," he said.

In theory, however, decidual cast formation can be expected when prolonged endometrial proliferation precedes progesterone exposure, leading to a thicker endometrial layer. When the progesterone levels falter, the likelihood of decidual cast formation may grow, he said.

Although these cases had varying scenarios, it is possible that similar hormonal events led to the decidual cast

formation and passage, he explained.

The first three patients had an extended period of amenorrhea with estrogen-only stimulation of the endometrial lining, and thus endometrial proliferation. The fourth patient also may have had prolonged estrogen production with resumption of ovarian estrogen production late in breast-feeding.

DMPA treatment in these patients would then have resulted in a high level of progesterone exposure followed by a gradual decline in progesterone levels that might have led to the decidual casts, he said.

In most of these cases, the decidual casts were, understandably, very frightening for the patient and/or parent, he said.

For this reason, as well as to fully inform patients about the potential effects of DMPA and to promote treatment compliance, patient counseling should include discussion of decidual cast expulsion as a rare side effect associated with the drug.

Furthermore, because 1% of DMPA failures are ectopic pregnancies (although DMPA is not a known cause of ectopic pregnancies), and because decidual casts and ectopic pregnancies can be easily confused, patients using DMPA who experience tissue passage should be advised to bring the specimen in for evaluation and should undergo a pregnancy test. ■



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DR. SCOTT

Study Sees No Link Between OC Use And Birth Defects

ST. PETE BEACH, FLA. — Periconceptual exposure to oral contraceptives was not associated with increased risk of adverse fetal outcomes in a recent prospective study.

None of the 45 women who were exposed to oral contraceptives during the periconceptual period and were followed until after delivery gave birth to an infant with congenital malformations, compared with 6 of 225 controls. The difference in the congenital malformation rate between the exposed and control groups was not significant, said H.K. Ahn, M.D., and colleagues of the Motherisk Program at Sungkyunkwan University, Seoul, South Korea, during a poster session at the annual meeting of the Teratology Society.

The groups were also similar in regard to mean gestational age at delivery (39 weeks in both groups) and birth weight (3,257 g in the exposed group, and 3,268 g in the controls), the investigators said.

Women in the exposed group took oral contraceptives containing either combined ethinyl estradiol and progesterone, or high-dose progesterone.

Although some earlier studies suggested a link between oral contraceptive use during pregnancy and increased risk of birth defects, later studies—including the current study—have failed to reproduce these findings.

"Exposure to oral contraceptives, including high doses of progesterone ... did not increase adverse fetal outcomes," the investigators said.

—Sharon Worcester